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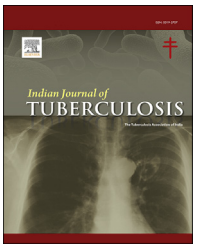

Review article

# Post covid 19 pulmonary fibrosis- Is it reversible?

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ABSTRACT

After the COVID-19 outbreak, increasing number of patients worldwide who have survived COVID-19 continue to battle the symptoms of the illness, long after they have been clinically tested negative for the disease. As we battle through this pandemic, the challenging part is to manage COVID-19 sequelae which may vary from fatigue and body aches to lung fibrosis. This review addresses underlying mechanism, risk factors, course of disease and treatment option for post covid pulmonary fibrosis. Elderly patient who require ICU care and mechanical ventilation are at the highest risk to develop lung fibrosis. Currently, no fully proven options are available for the treatment of post inflammatory COVID 19 pulmonary fibrosis.



## 1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic began in Wuhan, China, in December 2019, and has since then spread worldwide.[1] As of September 30, 2020, the cases of COVID-19 infection continues to soar worldwide with no peak in sight making total case tally standing at 63,12,585 including 9,40,705 active cases, 52,73,202 cured/discharged/migrated and 98,678 deaths, according to the Ministry of Health and Family Welfare. While whole medical fraternity and researchers across the world continue to learn more about the novel contagion and its bizarre array of symptoms, it is becoming clear that the battle with COVID-19 is not an easy one.

After the COVID-19 outbreak, increasing number of patients worldwide who have survived COVID-19 continue to battle the symptoms of the illness, long after they have been clinically tested negative for the disease. They are called as long – haulers. As we battle through this pandemic, the challenging part is how to manage this COVID-19 Sequelae which may vary from mild in terms of fatigue and body aches to severe forms requiring long term oxygen therapy and lung transplantation due to lung fibrosis, significant cardiac abnormalities and stroke leading to significant impairment in Quality of health. Various studies have reported that around 70–80% of patients who recovered from COVID-19 presents with persistence of at least 1 or more symptoms, even after being declared COVID-free.[2,3]

Considering millions of covid 19 cases worldwide, even small proportion of post covid lung fibrosis is worrisome. Many active clinical trials and studies are underway to know more about the entity post covid pulmonary fibrosis. This narrative review summarizes current clinical evidence regarding post COVID-19 pulmonary fibrosis.

## 2. Materials & Methods

This review was performed to address following questions for post covid pulmonary fibrosis.

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1. Mechanism
2. Risk factors
3. Clinical course
4. Treatment option

A literature review was performed using different database (PubMed, Scopus, Science Direct, and Google Scholar) to identify relevant English-language articles published through September 25,2020. Search terms included coronavirus, severe acute respiratory syndrome coronavirus 2, COVID-19, Post covid fibrosis, antifibrotic. The search resulted in 2,567 total articles. Due to the lack of RCTs, we have also included case reports, case series, and review articles. The authors independently reviewed the titles and abstracts for inclusion. Additional relevant articles were identified from the review of citations referenced. Active clinical trials were identified using the disease search term coronavirus infection on ClinicalTrials.gov.

### 2.1. *Mechanism of post COVID pulmonary fibrosis*

Various mechanisms of lung injury in COVID-19 have been described, with both viral and immune-mediated mechanisms being implicated.[4] Pulmonary fibrosis can be either subsequent to chronic inflammation or an idiopathic, genetically influenced and age related fibroproliferative process. Pulmonary fibrosis is a known sequela to ARDS. However, persistent radiological abnormalities after ARDS are of little clinical significance and have dwindled with protective lung ventilation.[5]

It has been found that 40% of patients with COVID-19 develop ARDS, and 20% of ARDS cases are severe.[6] The prevalence of post-COVID-19 fibrosis will become apparent with time, but early analysis from patients with COVID-19 on hospital discharge suggests that more than a third of recovered patients develop fibrotic abnormalities. The pathological feature of ARDS is diffuse alveolar damage (DAD) which is characterized by an initial acute inflammatory exudative phase with hyaline membranes, followed by an organizing phase and fibrotic phase.[7] Previous studies highlight that duration of disease is an important determinant for lung fibrosis post ARDS. This study showed that, 4% of patients with a disease duration of less than 1 week, 24% of patients with a disease duration of between weeks 1 and 3, and 61% of patients with a disease duration of greater than 3 weeks, developed fibrosis.

Cytokine storm caused by an abnormal immune mechanism may lead to initiation and promotion of pulmonary fibrosis. Epithelial and endothelial injury occurs in the inflammatory phase of ARDS due to dysregulated release of matrix metalloproteinases. VEGF and cytokines such as IL-6 and TNFα are also involved in the process of fibrosis. The reason remains unknown as to why certain individuals recover from such an insult, whereas others develop progressive pulmonary fibrosis due to accumulation of fibroblasts and myofibroblasts and excessive deposition of collagen.[8]

Although ARDS seems to be the main predictor of pulmonary fibrosis in COVID-19, several studies showed that covid induced ARDS is different (High and low elastance type) from the classical ARDS. CT findings in many covid cases are also not suggestive of classical ARDS. Along with, abnormal coagulopathy is another pathological feature of this disease. So, mechanism of pulmonary fibrosis in COVID-19 is different from that of IPF and other fibrotic lung diseases, especially with pathological findings pointing to alveolar epithelial cells being the site of injury, and not the endothelial cells.

### 2.2. *Risk factor*

One of the risk factors for the development of lung fibrosis in COVID-19 is **advanced age** and this finding is same as in MERS and SARS-CoV.[9–11]

Second risk factor is **increased disease severity** which includes comorbidities such as hypertension, diabetes, and coronary artery disease[12] and Lab findings like lymphopenia, leukocytosis, and elevated lactate dehydrogenase (LDH).[7] Serum LDH level has been used as a marker of disease severity following acute lung injury. It is an indicator of pulmonary tissue destruction and correlates with the risk of mortality. According to the World Health Organization, 80% of SARS-CoV-2 infections are mild, 14% develop severe symptoms, and 6% will become critically ill.

Third risk factor is **prolonged ICU stay and duration of mechanical ventilation**. While disease severity is closely related to the length of ICU stay, mechanical ventilation poses an additional risk of ventilator-induced lung injury (VILI). Abnormalities of pressure or volume settings underlie this injury leading to a release of proinflammatory modulators, worsening acute lung injury, and increased mortality or pulmonary fibrosis in survivors.[13]

**Smokers** are 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to need ICU admission and mechanical ventilation or die compared to nonsmokers.[14,15]

The World Health Organization (WHO) and the National Institute on **Alcohol Abuse** and Alcoholism (NIAAA) have issued communications warning people to avoid excessive drinking, saying it may increase COVID-19 susceptibility and severity. Alcohol use disorder increases the risk for complications of COVID-19.[16]

### 2.3. *Clinical course*

What proportion of covid 19 patients developed lung fibrosis remains speculative and should not be assumed without appropriate prospective study. But we can extract data from SARS and MERS pandemic. Zhanga et al[17] followed 71 SARS patients for 15 years and found 9.4% at beginning of study, 4.6% at one year and 3.2% patients after 15 years had pulmonary lesions visible on CT scans. Similar findings were reported for MERS also. The follow-up of 36 MERS patients for an average of 43 days showed that lung fibrosis developed in a significant number of convalescents, and risk was found highest among patients who were elderly, hospitalised with severe disease in ICU.[18] We have paucity of data for course of post covid pulmonary fibrosis. In one of the study[19] chest CT scan was performed on the last day before discharge, two weeks and four weeks after discharge. Compared with the last CT scan before discharge, the abnormalities (including focal/multiple GGO, consolidation, interlobular septal thickening,

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subpleural lines and irregular lines) in lungs were gradually absorbed in the first and second follow-ups after discharge. The lung lesions of 64.7% discharged patients were fully absorbed after 4-week follow-up. It indicated that the damage to lung tissue by COVID-19 could be reversible for the common COVID-19 patients. It also suggested that the prognosis of non-severe patients is favourable, and the clinical intervention should be conducted in time to prevent common COVID-19 patients from worsening to severe patients.

Another study[2] conducted at Italy (between April 2020 to May 2020) assessed persistent symptoms in 143 patients who were discharged from the hospital after recovery from COVID-19. Patients were assessed at a mean of 60.3 days after the initial onset of COVID-19 symptom; at the time of evaluation, only 18 (12.6%) were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was observed among 44.1% of patients. They also found that most common symptom persistent beyond discharge was fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%).

Another follow up study[20] which studied the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery enrolled 55 patients and found different degrees of radiological abnormalities in 39 patients. Blood Urea nitrogen concentration at admission was associated with the presence of CT abnormalities.

Many studies have shown that most common abnormality of lung function in discharged survivors with COVID-19 is impairment of diffusion capacity, followed by restrictive ventilatory defects, both associated with the severity of the disease[21,22] Both decreased alveolar volume and $K_{CO}$ contribute to the pathogenesis of impaired diffusion capacity.[23] At 3-months after discharge, residual abnormalities of pulmonary function were observed in 25.45% of the cohort which was lower than the abnormal pulmonary function in COVID-19 patients when discharged.[10] Lung function abnormalities were detected in 14 out of 55 patients and the measurement of D-dimer levels at admission may be useful in prediction of impaired diffusion defect.[16]

### 2.4. *Treatment of post COVID 19 pulmonary fibrosis*

Currently, no fully proven options are available for the treatment of post inflammatory COVID 19 pulmonary fibrosis. Various treatment strategies are under evaluation. It has been proposed that prolonged use of anti-viral, anti-inflammatory and anti-fibrotic drugs diminish the probability of development of lung fibrosis. However, it is yet to be ascertained whether early and prolonged use of antiviral agents may prevent remodeling of lung or which of the available antiviral is more effective. Though risk-benefit ratio should be assessed prior to use, prolonged low dose corticosteroid may prevent remodeling of lung in survivors.[24] Anti-fibrotic drugs, such as pirfenidone and nintedanib, have anti-inflammatory effects as well and thus they may be used even in the acute phase of COVID-19 pneumonia.[25] Pirfenidone exerts anti-fibrotic, anti-oxidative and anti-inflammatory effects. Pirfenidone could attenuate ARDS induced lung injury as it reduces LPS-induced acute lung injury and subsequent fibrosis by suppressing NLRP3 inflammasome activation.[26] There are few concerns regarding antifibrotic in acute phase. Many covid 19 patients have hepatic dysfunction in the form of raised transaminases and both antifibrotics pirfenidone and Nintedanib cause hepatotoxicity. Nintedanib is associated with increased risk of bleeding as most of the covid 19 patients are on anticoagulant.

Evidence is present regarding use of pirfenidone, azithromycin and prednisolone in the management of pulmonary fibrosis post-H1N1 ARDS, based on data from a case report of three patients.[27] Now the literature supports the use of antifibrotic by the first week of ARDS onset to prevent consequences such as lung fibrosis. Thus, there is urgent need for the identification of biomarkers early in the disease course to identify patients who are likely to progress to pulmonary fibrosis. The rationale for using antifibrotic therapy should be personalized and the role of precision medicine assumes prediction of high-risk population, better understanding of pathophysiology and prevention of disease worsening or/and lung fibrosis development.

Rehabilitation in the acute stage and particularly in the recovery stage is beneficial. It improves respiratory function, exercise endurance, self-care in daily living activities and psychological support.[28] However, scientific research is required for concluding its definite benefits.

## 3. Conclusion

Considering huge numbers of individuals affected by COVID-19, even rare complications like post covid pulmonary fibrosis will have major health effects at the population level. Elderly patient who require ICU care and mechanical ventilation are the highest risk to develop lung fibrosis. Currently, no fully proven options are available for the treatment of post inflammatory COVID 19 pulmonary fibrosis.

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## Conflicts of interest

The authors have none to declare.

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